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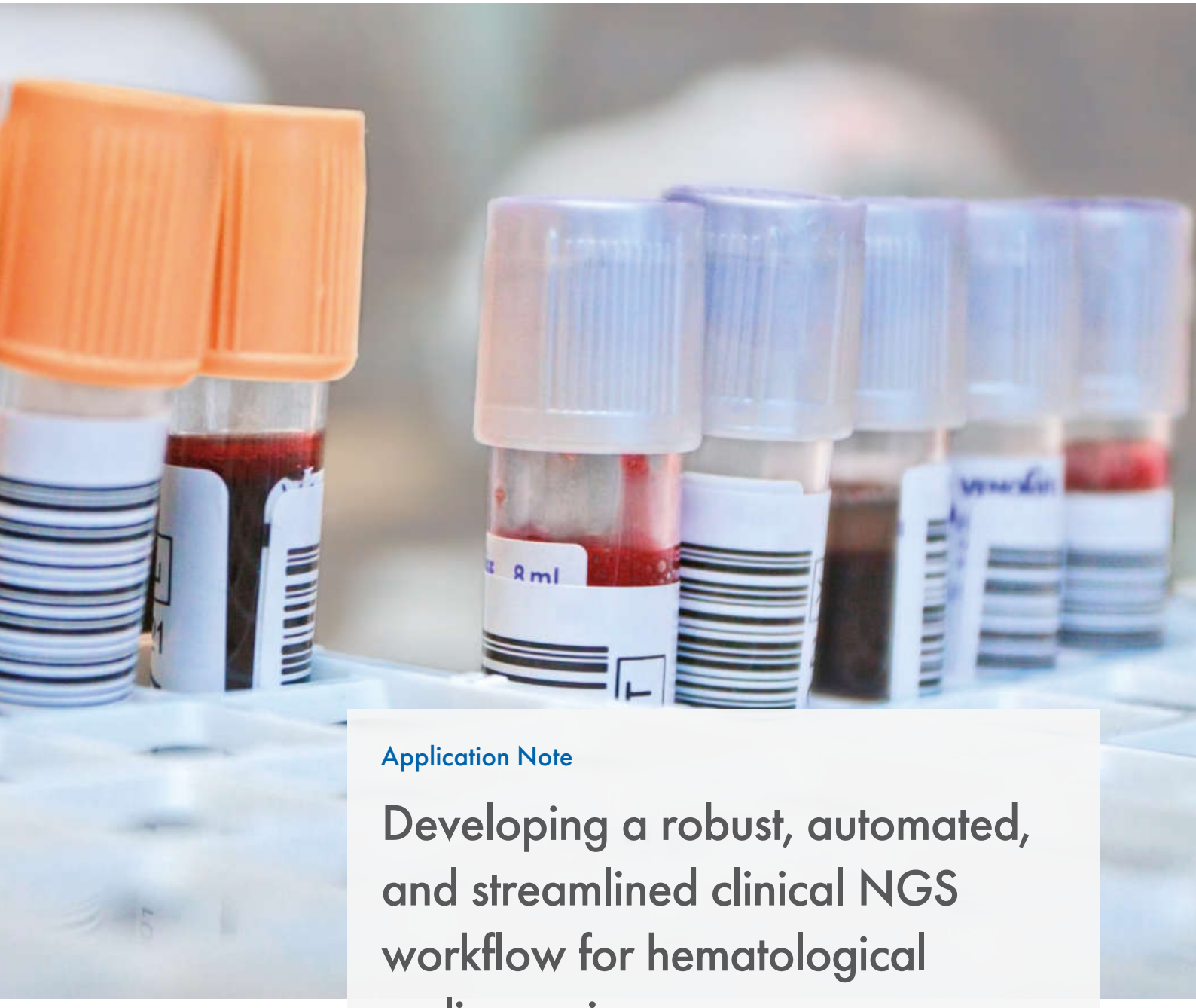
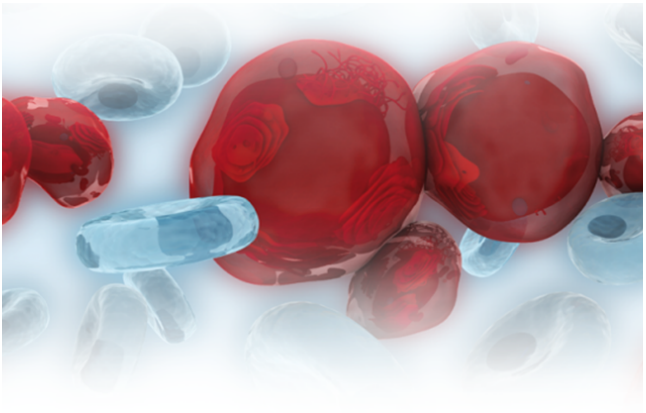


Application Note

Developing a robust, automated, and streamlined clinical NGS workflow for hematological malignancies

Sample to Insight



Next-generation sequencing (NGS) has transformed the field of oncology. Early successes in identifying and targeting oncogenic drivers of solid tumors have set the foundation for genomics-guided precision medicine; but, for hematological malignancies, the path to precision medicine is a lot more complex.

Within the hematologic oncology space, there is a spectrum of biologically related, but clinically heterogeneous diseases. In part, the differences between patients are driven by the particular combination of genetic mutations each disease acquires during its evolution. To effectively treat and manage myeloid malignancies, hematologist-oncologists need highly parallel, highly sensitive assays that (1) enable the simultaneous analysis of multiple genes and (2) are coupled with indication-specific bioinformatic pipelines that provide information on disease classification, prognostication, treatment selection, and monitoring.

Approximately 10% of new cancer cases diagnosed in the United States are classified as leukemia, lymphoma, and myeloma. In other terms, there are nearly 175,000 patients newly diagnosed each year who may benefit from diagnostic and prognostic insights elucidated by clinical NGS testing.

While NGS promises to help more patients with myeloid malignancies, there are several key obstacles that must be overcome. First, the clinical NGS workflow needs to be streamlined. In today's clinical NGS lab, pipelines are assembled with a variety of commercial and open-source products and solutions that cover everything from sample preparation to variant interpretation.

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Yet, fragmented workflows present inherent problems. When multiple products and soluti-

ns are used, manual data transfer becomes a necessity, leading to longer turnaround times and more opportunities for error. Further, pipelines built upon free, open-source tools are difficult to tailor, maintain, and scale. To improve results of NGS testing within the hematologic-oncology space, clinical routine diagnostics labs must implement an easy, seamless, and fully customizable workflow that is supported by a bioinformatic analysis tool capable of handling the clinical heterogeneity of myeloid malignancies.

Special attention must be paid in selecting the right bioinformatic solution and in further implementing it as part of a production environment. Choosing the wrong pipeline could substantially impact the ability to accurately and confidently detect all relevant variants, simple or complex. In addition, choosing the wrong pipeline could have serious implications on the ability to scale with growth. Pipelines should be automated and should be able to handle a high volume both now and in the future. The benefits brought about by automated sample prep all the way through variant interpretation and reporting result in a reduction in repetitive testing and higher confidence reporting of variants, ultimately reducing internal assay costs, minimizing risk and driving business growth.

Specific challenges for NGS in hemato-oncology

Implementing a complete, end-to-end NGS workflow is challenging enough, but successfully adopting a bioinformatics solution is one of today's biggest hurdles. Bioinformatic analyses span the assessment of raw data quality, preprocessing, alignment, post-processing, variant calling, annotation, filtering, interpretation, and reporting. Pipeline construction may require one solution for all, or one software per step. The decision to go one way or the other, and the selection of tools to work together, is critical as it may introduce errors or biases in the analysis.

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Beyond the pipeline, and specific to hemato-oncology, is the challenge of dealing with complex mutations that are highly relevant to

myeloid malignancies. The chemistry behind short read sequencing, which most labs use today, hampers the ability to sequence certain genes, due to the inherent complexity of the genomic locus or the type of mutation. This is especially true for the CEBPA locus, large clinically relevant insertions and deletions within genes, such as FLT3 and CALR, and chromosomal rearrangements. Providing a wholistic assessment that informs on pathogenicity and ultimately clinical decisions are usually done by integrating diverse data from multiple assays in addition to NGS. This is difficult for any lab professional and the consistency and reproducibility in how the results of these different assays are integrated and interpreted is heavily dependent on the relative body of experience the lab director has in each specific subclass.

Finally, the burden of manual curation is not to be minimized. Staying informed and up-to-date given the exponential growth of literature, the continual change in availability of clinical trials and updates in drug indications is key to providing a clear and accurate report with pathogenicity and actionability insights that can hopefully enable better outcomes. The increasing demand for NGS technologies in the clinic has led to an increase in the rate at which mutations are characterized for clinical utility, putting enormous pressure on the analysts responsible for manually searching each variant discovered.

Bioinformatics solutions for hematological malignancies

QIAGEN Clinical Insights (QCI®) offers a comprehensive and integrated portfolio of bioinformatics software and service solutions for routine diagnostic labs evaluating hematologic neoplasms.

QCI Precision Insights

A full-service offering within the QCI portfolio, QCI Precision Insights provides scalable, cost-effective genomic clinical decision support that delivers concise oncologist-reviewed evidence for each biomarker in the context of the cancer sub-type, listing information on the mutation's molecular characteristics, roles in disease, and therapeutic, prognostic, and diagnostic implications.

QCI Precision Insights' team of experts has interpreted more than 190,000 tumor samples for pathologists and lab directors. For the analysis of hematological cases, variant- and disease-specific clinical evidence, potential therapeutic options, as well as biomarker prognostic and diagnostic significance, where applicable, are reviewed and approved by a team of medical oncologists who practice across oncology sub-specialties, including hematology. This is of particular importance for co-occurring mutations in hematological malignancies, which can affect a patient's prognosis, diagnosis, and treatment outcome.

See how Quest Diagnostics uses QCI Precision Insights for rapid interpretation of their novel LeukoVantage assay at https://www.workcast.com/register?cpak=2294340257892161

QCI Interpret One

For routine diagnostic labs that do not have an in-house bioinformatics solution to prioritize and report variants, QCI Interpret One combines the flexible QIAGEN Clinical Insights software with the trusted services of N-of-One, a QIAGEN company and leading provider of somatic variant interpretation.

With QCI Interpret One, lab directors can prepare, prioritize and report on clinically relevant variants associated with hematological malignancies without the time-consuming step of researching and writing variant- and disease-specific evidence summaries. Users get access to an "expert second opinion" for variant classification, and they can deliver professional reports directly to physicians and oncologists to better inform clinical decision making.

"QIAGEN's new QCI Interpret One is impressive. It combines the former N-of-One interpretation summaries with QIAGEN's QCI Interpret structured variant interpretation database. No one is better than QIAGEN for Variant Interpretation."

Ravindra Kolhe, MD, PhD
Chief, Section of Molecular and Genetic Pathology, Augusta University

Looking ahead

The potential for improving diagnosis, prognosis, and treatment selections among patients with blood cancers is clear. By focusing on development of a robust, automated, and streamlined NGS analysis pipeline, we as a community can help broaden the reach of precision medicine for hundreds of thousands of patients in need.

The text of this application note is sourced from, "Clinical Genomics in Hematological Malignancies Require Streamlined Bioinformatics Solutions," written by Beate Litzenburger, PhD, Global Product Director of Oncology at QIAGEN Digital Insights, and published in Clinical Research News.

Learn more about QCI Interpret One and the QCI portfolio at
www.digitalinsights.qiagen.com/qci-interpret-one